Efecto del tratamiento antidepresivo sobre los síntomas cognitivos del Alzheimer

José María García-Alberca, MD, PhD

Prevalencia y comorbilidad de síntomas neuropsiquiátricos en la enfermedad de Alzheimer

García-Alberca, JM et al. 2008
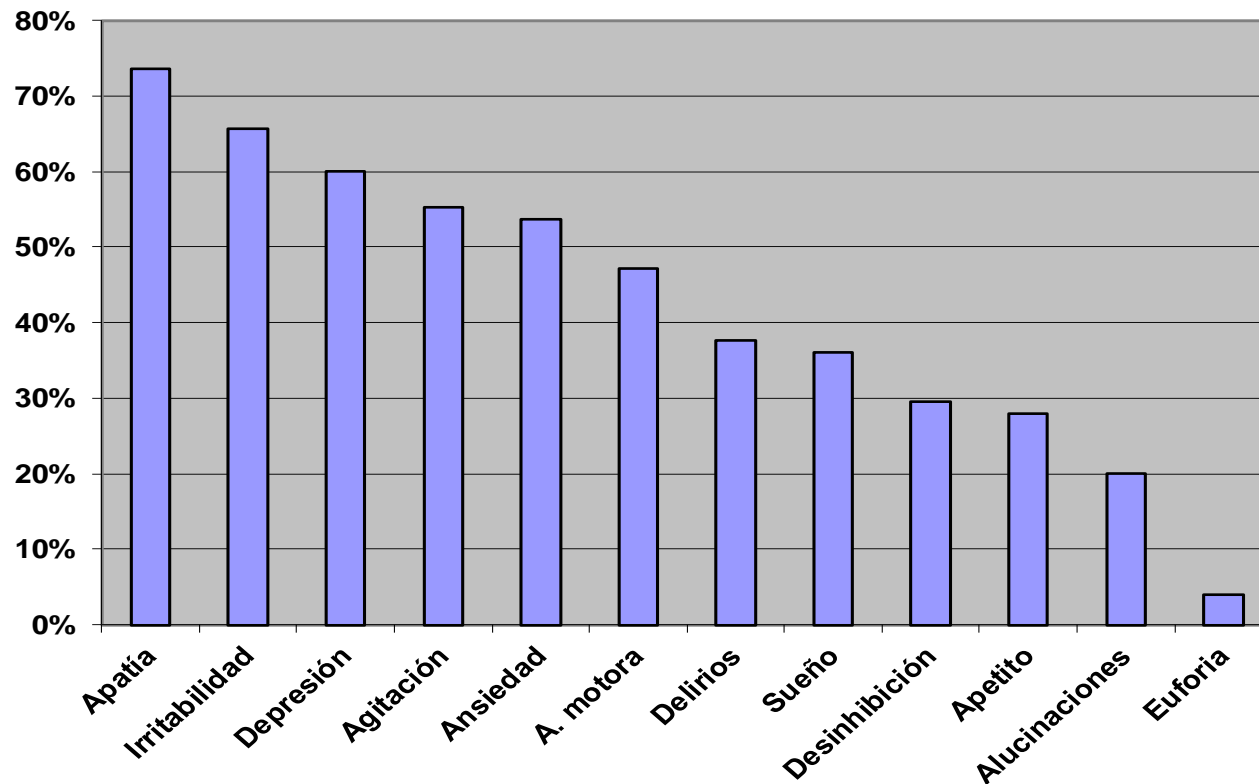
A Collaborative Study of the Emergence and Clinical Features of the Major Depressive Syndrome of Alzheimer's Disease

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Objective: This report provides a description of the prevalence and clinical features of the major depressive syndrome of Alzheimer's disease using data derived from structured diagnostic assessments of 243 patients with probable Alzheimer's disease and 151 nondemented elderly comparison subjects.

Method: Subjects were characterized by a consortium of four Alzheimer's disease research centers and the Geriatric Psychiatry Branch of the National Institute of Mental Health. All sites administered the Clinical Assessment of Depression in Dementia, a structured, anchored diagnostic interview that was developed to reliably diagnose and characterize major depressive episodes in this population.

Results: Despite the use of a common, reliable methodology for the assessment and diagnosis of major depressive episodes, the prevalence of major depression in Alzheimer's disease ranged widely from 22.5% to 54.4% across the recruitment sites. The prevalence of major depressive episodes among Alzheimer's disease patients in the aggregate sample exceeded that for elderly comparison subjects and reached nearly 50% among the most severely demented patients. Alzheimer's disease patients with a current major depressive episode had earlier mean ages at onset, a higher mean Hamilton Depression Rating Scale score, and were more likely to be experiencing psychotic symptoms than those who had not developed a major depressive episode. Although the major depressive episodes of Alzheimer's disease patients and nondemented elderly comparison subjects included similar numbers of depressive symptoms, patients with Alzheimer's disease were more likely to report a diminished ability to concentrate or indecisiveness and less likely to experience sleep disturbances and feelings of worthlessness or excessive guilt during their major depressive episodes. None of the clinical features of major depression differed significantly in frequency among depressed Alzheimer's disease patients with mild, moderate, or severe dementia. Concurrent psychotic symptoms progressively increased with dementia severity.

Conclusions: The high rate of major depressive episodes that occur after the onset of cognitive impairment among patients with Alzheimer's disease (the majority of whom had no premorbid history of major depression), common emergence in the early stages of dementia when symptoms of cognitive impairment are least likely to contribute to the syndromal diagnosis of major depression, and differences in the clinical presentations of the major depressive episodes of Alzheimer's disease patients and nondemented elderly comparison subjects, all support the validity of the major depressive syndrome of Alzheimer's disease. Our findings suggest that the major depressive syndrome of Alzheimer's disease may be among the most common mood disorders of older adults.

Depresión y Alzheimer: consecuencias

- Deterioro cognitivo más rápido

- Pérdida de calidad de vida

- Mayor consumo de psicofármacos

- Incremento costes asistenciales

- Limitación AVD

- Institucionalización prematura

- Mayor carga del cuidador

- Mayor mortalidad

Holtzer et al 2005; Tatsumi et al 2009; García-Alberca 2017; Livingston et al 2020

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Cognitive impairments and depression: a critical review

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2015

Table 1		Systematic reviews and meta-analyses on depression and cognitive impairments (2004–2014)		
Author	**Year**	**Clinical aspects**	**Cognitive domains**	**Studies included**
Porter et al.[23]	2007	Severity of depression, Melancholic subtype, Age and Pharmacotherapy	Attention, Verbal and non-verbal memory, and Executive functions	20
Castaneda et al.[8]	2008	Severity of depression, and Anxiety disorders	Executive functions, Working memory, Verbal learning and memory	9
McDermott et al.[11]	2009	Severity of depression	Executive functions, Memory, and Processing speed	69
McClintock et al.[22]	2010	Severity of depression, and Number of previous episodes	Executive functions, Attention, and Memory	35
Hasselbach et al.[15]	2011	Remission in unipolar depression	Attention, Executive functions Memory, and Learning	11
Wagner et al.[4]	2012	Severity of depression, and comparison with healthy controls	Executive functions	15
Lee et al.[12]	2012	Patients with a first depressive episode	Psychomotor speed, Attention, Working memory, Verbal learning and memory, Visual learning and memory, cognitive flexibility, Verbal fluency, and attentional flexibility	13
Bora et al.[13]	2013	Age of onset, and comparison with healthy controls	Executive functions, Working memory, Attention, verbal and visual memory, and Processing speed	27
Rock et al.[2]	2013	Acute phase of the depression and clinical remission	Executive functions, and CANTAB*	24
Snyder[3]	2013	Age of patient, severity, and pharmacotherapy	Executive functions	113
Baune et al.[9]	2014	Depressed patients ages 12 to 25 years	Executive functions, Memory, Attention, Psychomotor speed, and Processing speed	7
Trivedi et al.[1]	2014	Pharmacotherapy	Executive functions, Learning, and Memory	12

*CANTAB (Cambridge Neuropsychological Test Automated Battery): Memory, Attention and Reaction time in cognitive tasks

Neuroplasticity in cognitive and psychological mechanisms of depression: An integrative model

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Abstract

Chronic stress and depressive-like behaviors in basic neuroscience research have been associated with impairments of neuroplasticity, such as neuronal atrophy and synaptic loss in the medial prefrontal cortex (mPFC) and hippocampus. The current review presents a novel integrative model of neuroplasticity as a multi-domain neurobiological, cognitive, and psychological construct relevant in depression and other related disorders of negative affect (e.g., anxiety). We delineate a working conceptual model in which synaptic plasticity deficits described in animal models are integrated and conceptually linked with human patient findings from cognitive science and clinical psychology. We review relevant reports including neuroimaging findings (e.g., decreased functional connectivity in prefrontal-limbic circuits), cognitive deficits (e.g., executive function and memory impairments), affective information processing patterns (e.g., rigid, negative biases in attention, memory, interpretations, and self-associations), and patient-reported symptoms (perseverative, inflexible thought patterns; inflexible and maladaptive behaviors). Finally, we incorporate discussion of integrative research methods capable of building additional direct empirical support, including using rapid-acting treatments (e.g., ketamine) as a means to test this integrative model by attempting to simultaneously reverse these deficits across levels of analysis.

Translational Psychiatry

Clinical research
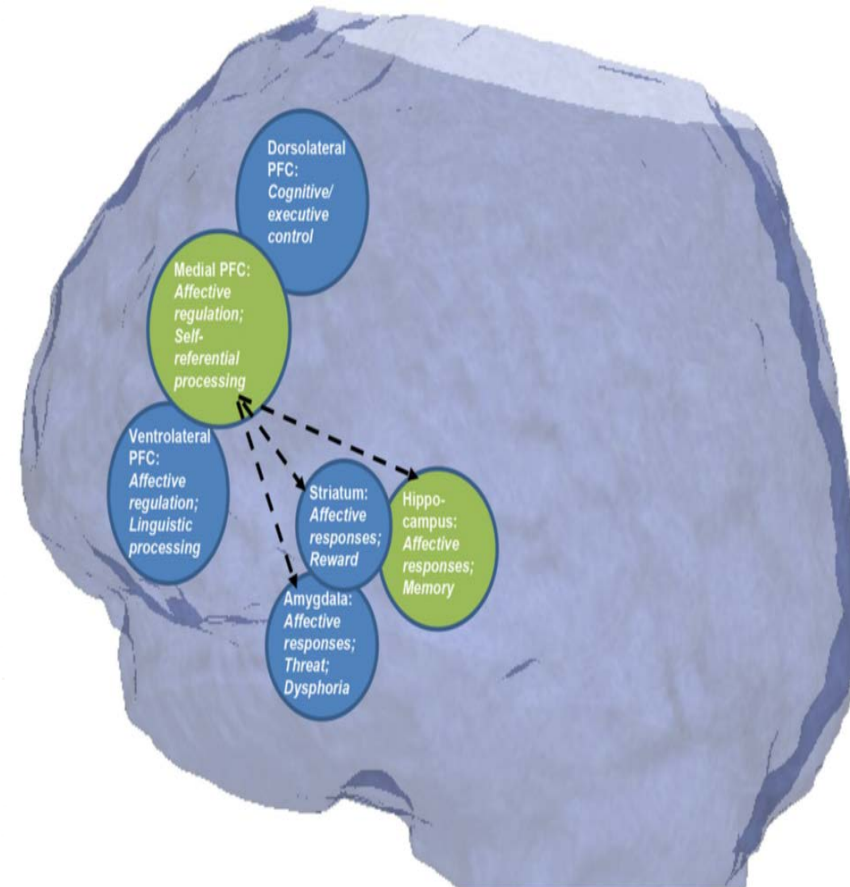
Mechanisms and treatment of late-life depression

George S. Alexopoulos[1]

Pathways linking late-life depression to persistent cognitive impairment and dementia

Meryl A. Butters, PhD; Jeffrey B. Young, BA; Oscar Lopez, MD; Howard J. Aizenstein, MD, PhD; Benoit H. Mulsant, MD; Charles F. Reynolds III, MD; Steven T. DeKosky, MD; James T. Becker, PhD
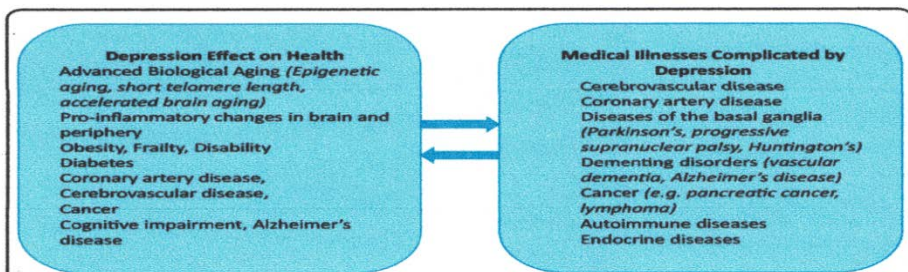
Fig. 1 Reciprocal relationship of depression and medical health

Depression Effect on Health
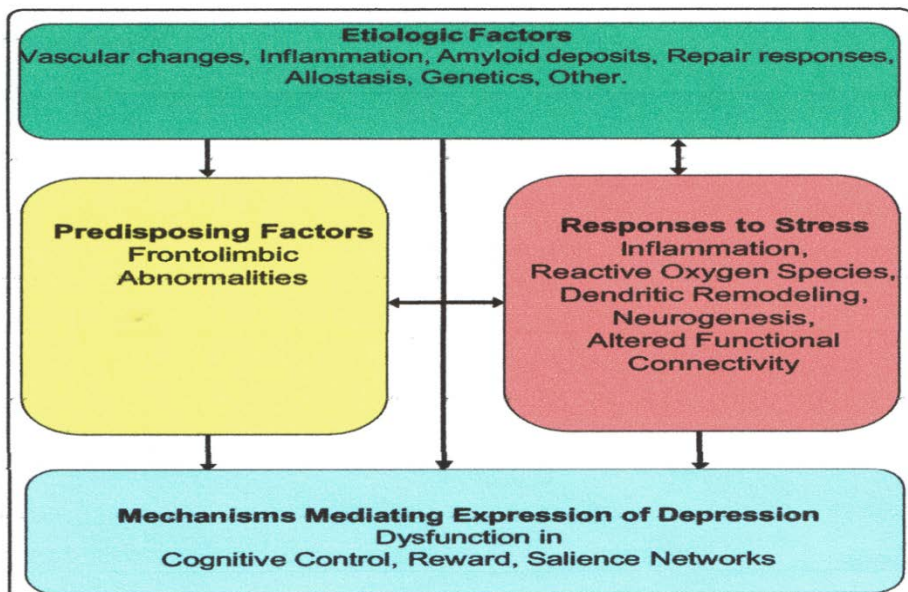Advanced Biological Aging *(Epigenetic aging, short telomere length, accelerated brain aging)*
Pro-inflammatory changes in brain and periphery
Obesity, Frailty, Disability
Diabetes
Coronary artery disease,
Cerebrovascular disease,
Cancer
Cognitive impairment, Alzheimer's disease

Medical Illnesses Complicated by Depression
Cerebrovascular disease
Coronary artery disease
Diseases of the basal ganglia *(Parkinson's, progressive supranuclear palsy, Huntington's)*
Dementing disorders *(vascular dementia, Alzheimer's disease)*
Cancer *(e.g. pancreatic cancer, lymphoma)*
Autoimmune diseases
Endocrine diseases

Fig. 2 Working model of late-life depression

Etiologic Factors
Vascular changes, Inflammation, Amyloid deposits, Repair responses, Allostasis, Genetics, Other.

Predisposing Factors
Frontolimbic Abnormalities

Responses to Stress
Inflammation,
Reactive Oxygen Species,
Dendritic Remodeling,
Neurogenesis,
Altered Functional Connectivity

Mechanisms Mediating Expression of Depression
Dysfunction in
Cognitive Control, Reward, Salience Networks

Depression
Glucocorticoids
Cerebrovascular disease
Hippocampal atrophy
Generalized ischemia
Frontostriatal abnormalities
↓ Brain/cognitive reserve
AD causal factors
AD pathology
Clinical AD

Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review

Comparative Effectiveness Review
Number 46

Background: Depressive disorders such as major depressive disorder (MDD), dysthymia, and subsyndromal depression may be serious disabling illnesses. MDD affects more than 16 percent of adults at some point during their lifetimes. Second-generation antidepressants dominate the medical management of depressive disorders. These drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other drugs with related mechanisms of action that selectively target neurotransmitters.

Objectives: The objective of this report was to compare the benefits and harms of bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine for the treatment of depressive disorders, including variations of effects in patients with accompanying symptoms and patient subgroups.

Data Sources: We updated a comparative effectiveness review published in 2007 by the Agency for Healthcare Research and Quality searching PubMed, Embase, The Cochrane Library, and International Pharmaceutical Abstracts up to January 2011.

Review Methods: Two people independently reviewed the literature, abstracted data, and rated the risk of bias. If data were sufficient, we conducted meta-analyses of head-to-head trials of the relative benefit of response to treatment. In addition, we conducted mixed treatment comparisons to derive indirect estimates of the comparative efficacy among all second-generation antidepressants.

Results: From a total of 3,722 citations, we identified 248 studies of good or fair quality. Overall, no substantial differences in efficacy could be detected among second-generation antidepressants for the treatment of acute-phase MDD. Statistically significant differences in response rates between some drugs are small and likely not clinically relevant. No differences in efficacy were apparent in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbidities, although evidence within these subpopulations was limited.

Differences exist in the incidence of specific adverse events and the onset of action. Venlafaxine leads to higher rates of nausea and vomiting, sertraline to higher rates of diarrhea, and mirtazapine to higher rates of weight gain than comparator drugs. Bupropion causes lower rates of sexual dysfunction than other antidepressants. The evidence is insufficient to draw conclusions about the comparative efficacy and effectiveness for the treatment of dysthymia and subsyndromal depression.

Conclusions: Our findings indicate that the existing evidence does not warrant the choice of one second-generation antidepressant over another based on greater efficacy and effectiveness. Differences with respect to onset of action and adverse events may be taken into consideration for the choice of a medication.

OXFORD

REVIEW

The Cognitive Effects of Antidepressants in Major Depressive Disorder: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Joshua D Rosenblat, MD; Ron Kakar, MD; Roger S McIntyre, MD, FRCPC

Abstract

Background: Cognitive dysfunction is often present in major depressive disorder (MDD). Several clinical trials have noted a pro-cognitive effect of antidepressants in MDD. The objective of the current systematic review and meta-analysis was to assess the pooled efficacy of antidepressants on various domains of cognition in MDD.
Methods: Trials published prior to April 15, 2015, were identified through searching the Cochrane Central Register of Controlled Trials, PubMed, Embase, PsychINFO, Clinicaltrials.gov, and relevant review articles. Data from randomized clinical trials assessing the cognitive effects of antidepressants were pooled to determine standard mean differences (SMD) using a random-effects model.
Results: Nine placebo-controlled randomized trials (2 550 participants) evaluating the cognitive effects of vortioxetine (n = 728), duloxetine (n = 714), paroxetine (n = 23), citalopram (n = 84), phenelzine (n = 28), nortryptiline (n = 32), and sertraline (n = 49) were identified. Antidepressants had a positive effect on psychomotor speed (SMD 0.16; 95% confidence interval [CI] 0.05–0.27; I2 = 46%) and delayed recall (SMD 0.24; 95% CI 0.15–0.34; I2 = 0%). The effect on cognitive control and executive function did not reach statistical significance. Of note, after removal of vortioxetine from the analysis, statistical significance was lost for psychomotor speed. Eight head-to-head randomized trials comparing the effects of selective serotonin reuptake inhibitors (SSRIs; n = 371), selective serotonin and norepinephrine reuptake inhibitors (SNRIs; n = 25), tricyclic antidepressants (TCAs; n = 138), and norepinephrine and dopamine reuptake inhibitors (NDRIs; n = 46) were identified. No statistically significant difference in cognitive effects was found when pooling results from head-to-head trials of SSRIs, SNRIs, TCAs, and NDRIs. Significant limitations were the heterogeneity of results, limited number of studies, and small sample sizes.
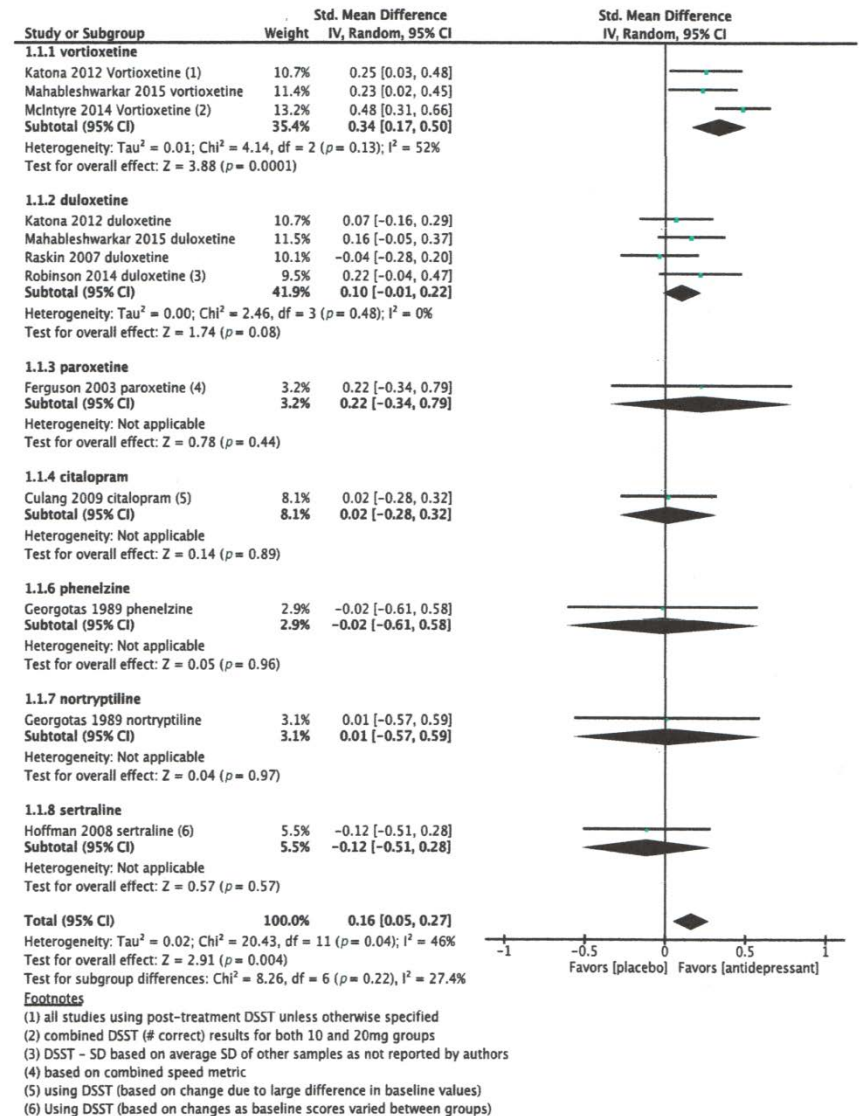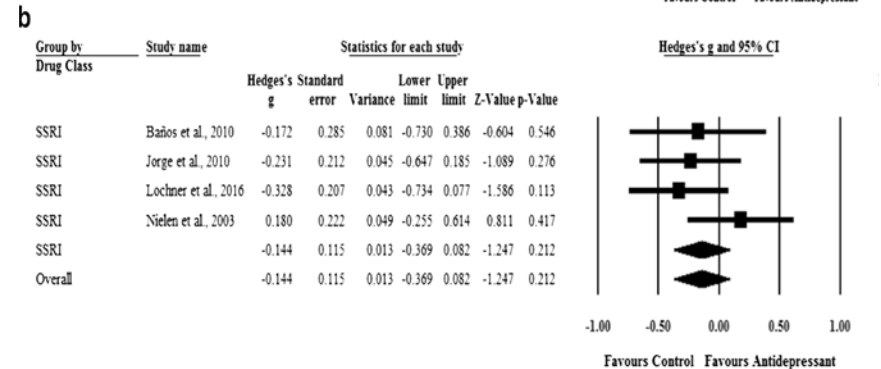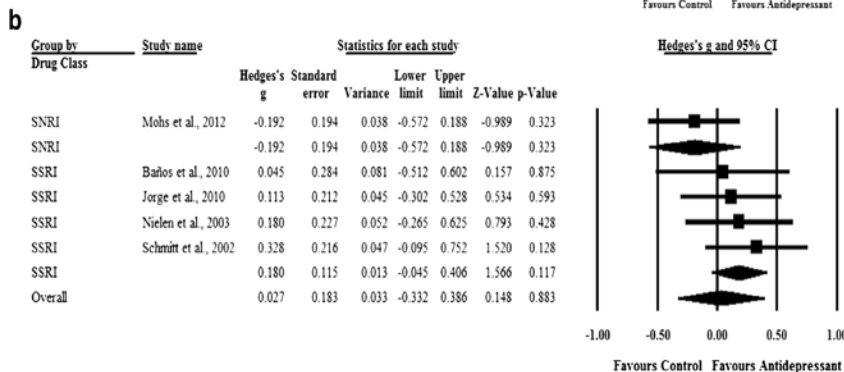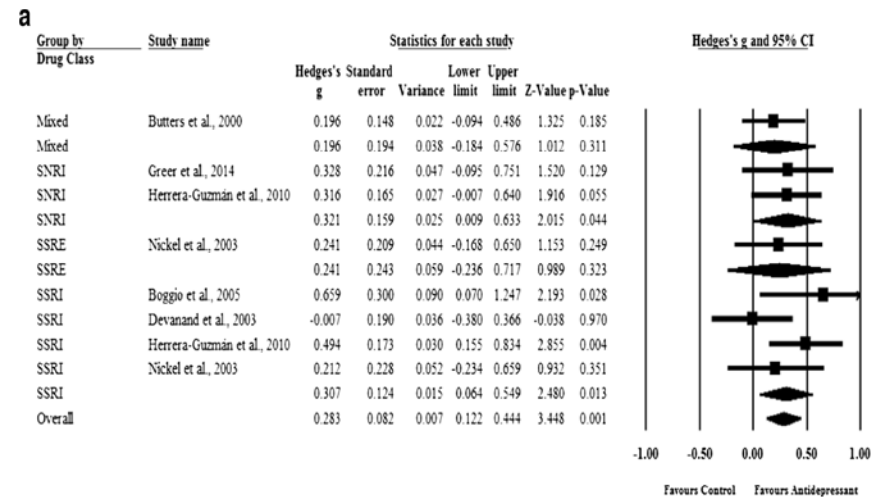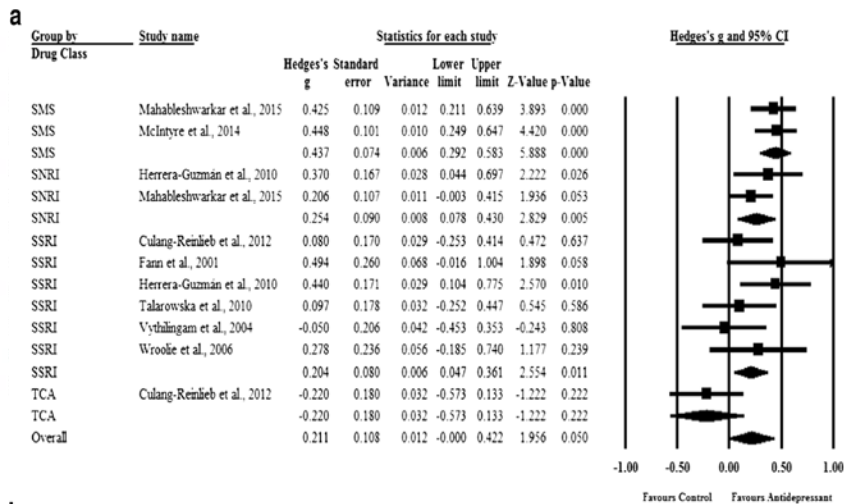

Figure 2. Pooled effect for placebo-controlled trials assessing psychomotor speed. CI, confidence interval; DSST, Digit Symbol Sign Test; SD, standard definiti...

REVIEW

CrossMark

A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples

Catherine E. Prado[1] · Stephanie Watt[1] · Simon F. Crowe[1]

a

Group by Drug Class	Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Hedges's g and 95% CI
SMS	Mahableshwarkar et al., 2015	0.425	0.109	0.012	0.211	0.639	3.893	0.000	
SMS	McIntyre et al., 2014	0.448	0.101	0.010	0.249	0.647	4.420	0.000	
SMS		0.437	0.074	0.006	0.292	0.583	5.888	0.000	
SNRI	Herrera-Guzmán et al., 2010	0.370	0.167	0.028	0.044	0.697	2.222	0.026	
SNRI	Mahableshwarkar et al., 2015	0.206	0.107	0.011	-0.003	0.415	1.936	0.053	
SNRI		0.254	0.090	0.008	0.078	0.430	2.829	0.005	
SSRI	Culang-Reinlieb et al., 2012	0.080	0.170	0.029	-0.253	0.414	0.472	0.637	
SSRI	Fann et al., 2001	0.494	0.260	0.068	-0.016	1.004	1.898	0.058	
SSRI	Herrera-Guzmán et al., 2010	0.440	0.171	0.029	0.104	0.775	2.570	0.010	
SSRI	Talarowska et al., 2010	0.097	0.178	0.032	-0.252	0.447	0.545	0.586	
SSRI	Vythilingam et al., 2004	-0.050	0.206	0.042	-0.453	0.353	-0.243	0.808	
SSRI	Woolie et al., 2006	0.278	0.236	0.056	-0.185	0.740	1.177	0.239	
SSRI		0.204	0.080	0.006	0.047	0.361	2.554	0.011	
TCA	Culang-Reinlieb et al., 2012	-0.220	0.180	0.032	-0.573	0.133	-1.222	0.222	
TCA		-0.220	0.180	0.032	-0.573	0.133	-1.222	0.222	
Overall		0.211	0.108	0.012	-0.000	0.422	1.956	0.050	

Favours Control   Favours Antidepressant

b

Group by Drug Class	Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Hedges's g and 95% CI
SNRI	Mohs et al., 2012	-0.192	0.194	0.038	-0.572	0.188	-0.989	0.323	
SNRI		-0.192	0.194	0.038	-0.572	0.188	-0.989	0.323	
SSRI	Baños et al., 2010	0.045	0.284	0.081	-0.512	0.602	0.157	0.875	
SSRI	Jorge et al., 2010	0.113	0.212	0.045	-0.302	0.528	0.534	0.593	
SSRI	Nielen et al., 2003	0.180	0.227	0.052	-0.265	0.625	0.793	0.428	
SSRI	Schmitt et al., 2002	0.328	0.216	0.047	-0.095	0.752	1.520	0.128	
SSRI		0.180	0.115	0.013	-0.045	0.406	1.566	0.117	
Overall		0.027	0.183	0.033	-0.332	0.386	0.148	0.883	

Favours Control   Favours Antidepressant

a

Group by Drug Class	Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Hedges's g and 95% CI
Mixed	Butters et al., 2000	0.196	0.148	0.022	-0.094	0.486	1.325	0.185	
Mixed		0.196	0.194	0.038	-0.184	0.576	1.012	0.311	
SNRI	Greer et al., 2014	0.328	0.216	0.047	-0.095	0.751	1.520	0.129	
SNRI	Herrera-Guzmán et al., 2010	0.316	0.165	0.027	-0.007	0.640	1.916	0.055	
SNRI		0.321	0.159	0.025	0.009	0.633	2.015	0.044	
SSRE	Nickel et al., 2003	0.241	0.209	0.044	-0.168	0.650	1.153	0.249	
SSRE		0.241	0.243	0.059	-0.236	0.717	0.989	0.323	
SSRI	Boggio et al., 2005	0.659	0.300	0.090	0.070	1.247	2.193	0.028	
SSRI	Devanand et al., 2003	-0.007	0.190	0.036	-0.380	0.366	-0.038	0.970	
SSRI	Herrera-Guzmán et al., 2010	0.494	0.173	0.030	0.155	0.834	2.855	0.004	
SSRI	Nickel et al., 2003	0.212	0.228	0.052	-0.234	0.659	0.932	0.351	
SSRI		0.307	0.124	0.015	0.064	0.549	2.480	0.013	
Overall		0.283	0.082	0.007	0.122	0.444	3.448	0.001	

Favours Control   Favours Antidepressant

b

Group by Drug Class	Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Hedges's g and 95% CI
SSRI	Baños et al., 2010	-0.172	0.285	0.081	-0.730	0.386	-0.604	0.546	
SSRI	Jorge et al., 2010	-0.231	0.212	0.045	-0.647	0.185	-1.089	0.276	
SSRI	Lochner et al., 2016	-0.328	0.207	0.043	-0.734	0.077	-1.586	0.113	
SSRI	Nielen et al., 2003	0.180	0.222	0.049	-0.255	0.614	0.811	0.417	
SSRI		-0.144	0.115	0.013	-0.369	0.082	-1.247	0.212	
Overall		-0.144	0.115	0.013	-0.369	0.082	-1.247	0.212	

Favours Control   Favours Antidepressant

Procognitive Effects of Antidepressants and Other Therapeutic Agents in Major Depressive Disorder: A Systematic Review

Michelle J. Blumberg, BScH[a]; Sophie R. Vaccarino, BScH[a,b,*]; and Shane J. McInerney, MD, MB, MSc, MRCPsych[a,c,d,e]

Abstract

Objective: To review the efficacy of antidepressants and other therapeutic agents for the treatment of cognitive impairment in adults with major depressive disorder (MDD).

Data sources: We conducted a database search of MEDLINE, PsycINFO, and Embase through Ovid on May 7, 2019. The year of publication was not restricted. The search terms "Major Depressive Disorder," "depress*," "cognit*," and "therapeutics" were used.

Study selection: The studies included in this review were clinical trials of antidepressants and other therapeutic agents in MDD populations. Participants were aged between 18 and 65 years and had a DSM-III, -IV, or -5 diagnosis of MDD. In total, 2,045 research papers were screened, 53 full-text articles were assessed, and 26 articles were eligible to be included in this systematic review.

Data extraction: The data and quality of research papers were assessed and screened by 2 independent reviewers. Discrepancies were resolved through a third reviewer.

Results: Overall, studies demonstrated that tricyclic antidepressants do not have procognitive effects, while vortioxetine and bupropion have demonstrated procognitive effects in MDD populations relative to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Several non-antidepressant agents, such as modafinil, amphetamines, and erythropoietin, have also demonstrated significant positive effects on cognition in depression.

Conclusions: Present-day antidepressants and other agents have demonstrated procognitive effects in MDD, but the findings between various agents are mixed. Further research looking at objective measures of cognitive performance would be helpful to obtain more definitive results regarding the efficacy of therapeutics for cognitive impairment in MDD

Figure 2. Number of Participants That Completed Each Study
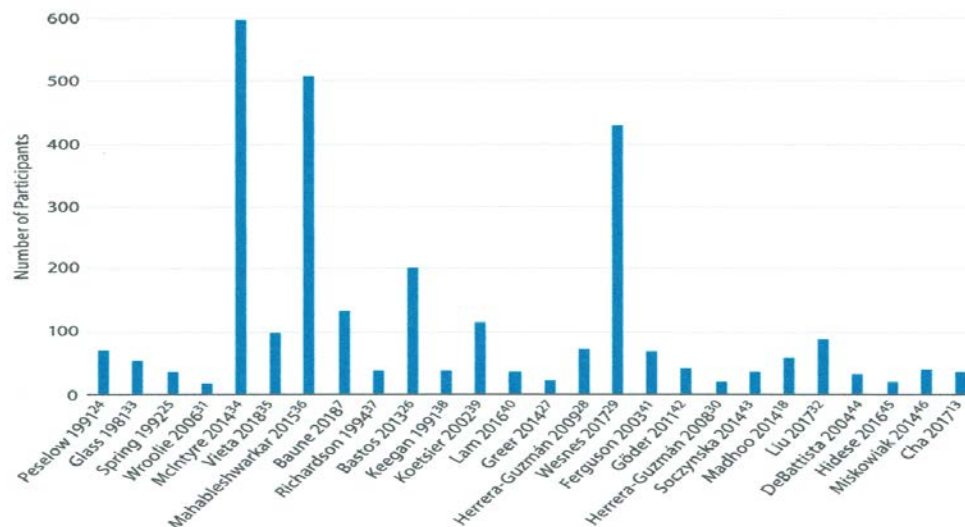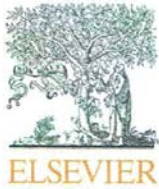
Research update

Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs

CrossMark

Elena Dale [a,*], Benny Bang-Andersen [b], Connie Sánchez [a]

Emerging Treatment Mechanisms for Depression: Focus on Glutamate and Synaptic Plasticity

Danielle M. Gerhard[a], Eric S. Wohleb[b], and Ronald S. Duman[b]

Review

Molecular Basis of Late-Life Depression

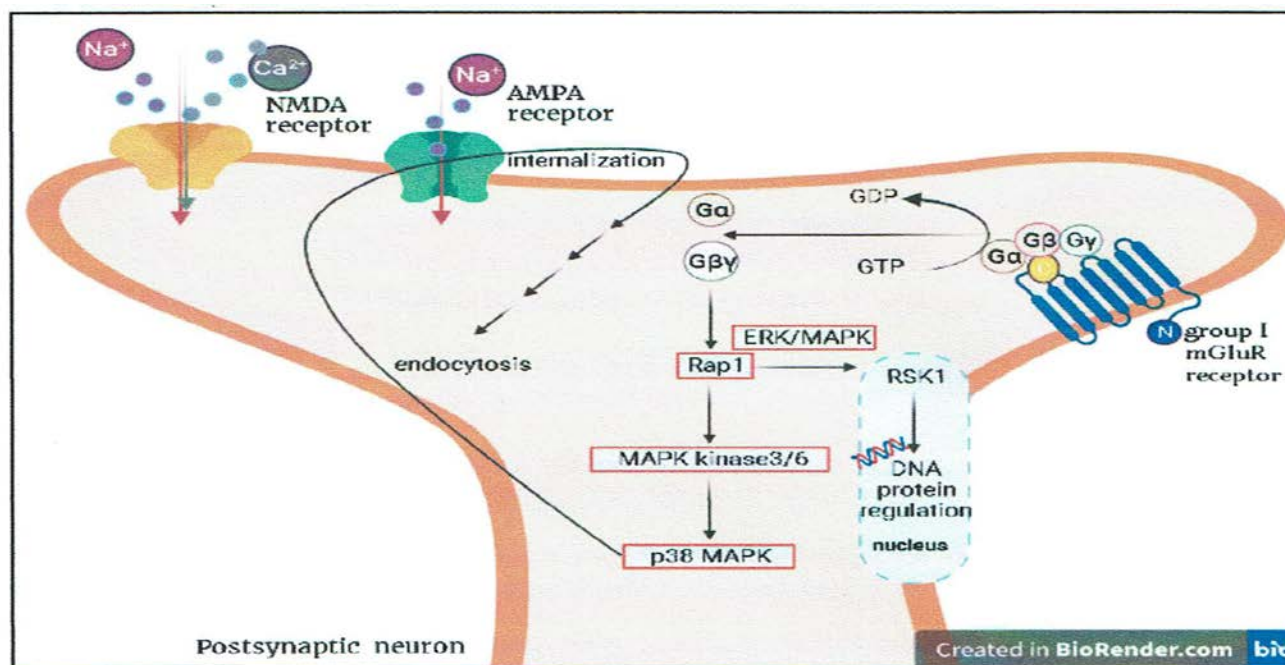Chien-Yi Kuo [1], Chieh-Hsin Lin [2,3,4,*] and Hsien-Yuan Lane [1,2,5,*]

2021

Figure 1. Signal pathway involved in mGluR–LTD. Metabotropic receptors (mGluRs) are G protein-coupled receptors. G proteins are activated when GTP is converted to GDP, and the three subunits (α, β, and γ) are dissociated. The release of G β and γ subunits activates Rap 1 and MAPK kinase 3/6. Subsequently, P38 MAPK, after it is activated, promotes AMPA receptor internalization and endocytosis. Additionally, the Rap 1–MAPK/ERK pathway activates nuclear protein RSK1. MAPK: mitogen-activated protein kinases; ERK: extracellular signal-regulated kinases; RSK1: ribosomal S6 kinase-1.

Opioid system modulation of cognitive affective bias: implications for the treatment of mood disorders

Bardia Varastehmoradi[a], Gregers Wegener[b], Connie Sanchez[a,b] and Karen L. Smith[b]
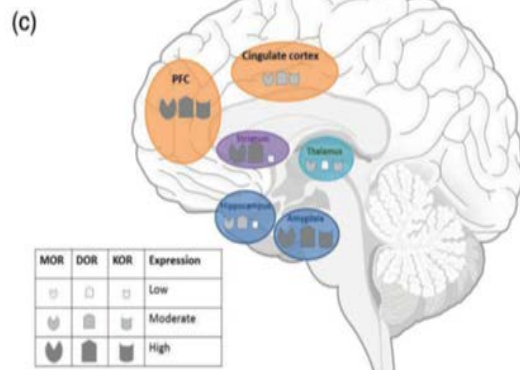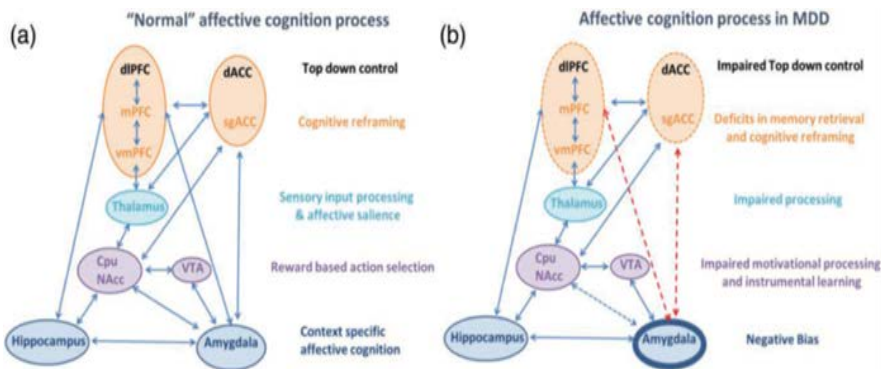

Table 1 Clinical evidence supporting opioid dysfunction in major depressive disorder

Measurement	Sample	Brain region of interest	Analysis method	Main outcomes	Ref
MOR expression	Post mortem suicide completers	PFC	RT-PCR	MOR expression is increased in suicide victims. Increased expression of alpha2A adrenoreceptors, 5HT1A, 5HT2A serotonin receptors	Escribá et al. (2004)
MOR density	Post mortem suicide completers	Frontal cortex Caudate nucleus	Quantitative autoradiography	Increased MOR density	Gabilondo et al. (1995)
MOR density	Post mortem suicide completers	PFC Temporal cortical gyri	Quantitative autoradiography	Increased MOR density. Age effect observed. In young victims, the MOR density is 9-fold higher in young completers compared to aged.	Gross-Isserof et al. (1995)
β Endorphin levels	Post mortem suicide completers	Left temporal cortex Left frontal cortex Left caudate nucleus	HPLC and Protein determination by Lwry method	β endorphin levels are decreased	Scarone et al. (1990)
μ opioid tone	MDD patients	vlPFC	PET scan	Negative correlation between positive emotionality and MOR binding potential	Light et al. (2017)
MOR availability		Rostral anterior cingulate Ventral pallidum Amygdala Inferior temporal cortex	PET scan	Sadness associated decreased MOR binding potential	Zubieta et al. (2003)
MOR availability	MDD patients	Rostral anterior cingulate Anterior insular cortex Anterior and posterior thalamus Ventral basal ganglia Amygdala Periamygdalar cortex Hypothalamus	PET scan	decreased MOR binding potential correlated to negative affect ratings during sadness. Increased Cortisol and Corticotropin level in plasma	Kennedy et al. (2006)
Prodynorphin	Suicide completers	Caudate nucleus	In situ hybridization histochemistry	Increased Prodynorphin mRNA expression	Hurd et al. (1997)
Prodynorphin	MDD patients	Amygdala	In situ hybridization histochemistry	Decreased Prodynorphin mRNA expression	Hurd et al. (2002)
OPRK1 mRNA	MDD patients	Cingulate cortex dlPFC	In situ hybridization histochemistry	No significant differences in OPRK1 mRNA expression between MDD patients and control group	Peckys and Hurd (2001)

dlPFC, dorsolateral prefrontal cortex; MDD, major depressive disorder; PFC, prefrontal cortex; vlPFC, ventrolateral prefrontal cortex.

725

Efficacy of Antidepressants for Depression in Alzheimer's Disease: Systematic Review and Meta-Analysis

2017

Vasiliki Orgeta*, Naji Tabet, Ramin Nilforooshan and Robert Howard
University College London, Brighton and Sussex Medical School and Surrey and Borders Partnership NHS Foundation Trust, London, UK
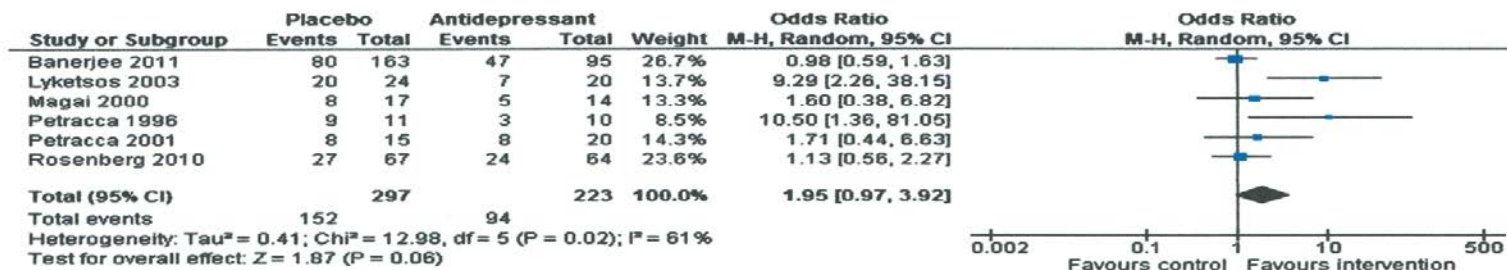

Fig. 2. Forest plot of comparison of antidepressants versus placebo: Response to treatment (6–13 weeks).
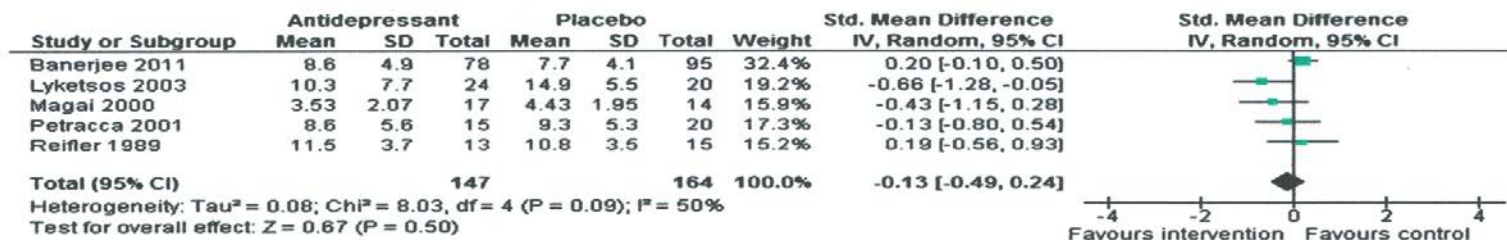

Fig. 3. Forest plot of comparison of antidepressants versus placebo: Mean depression scores (6–13 weeks).
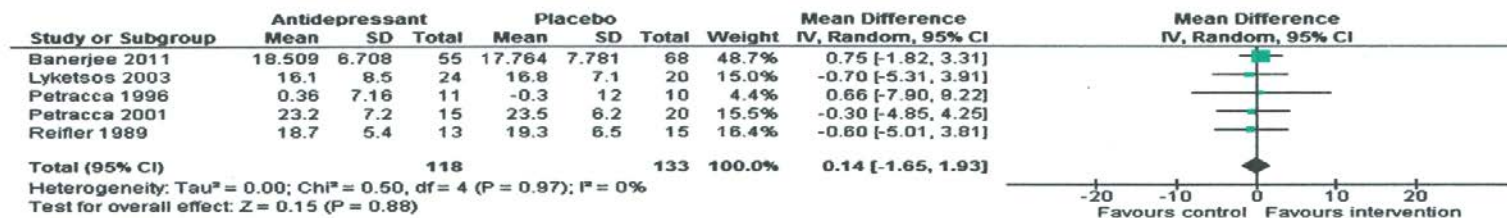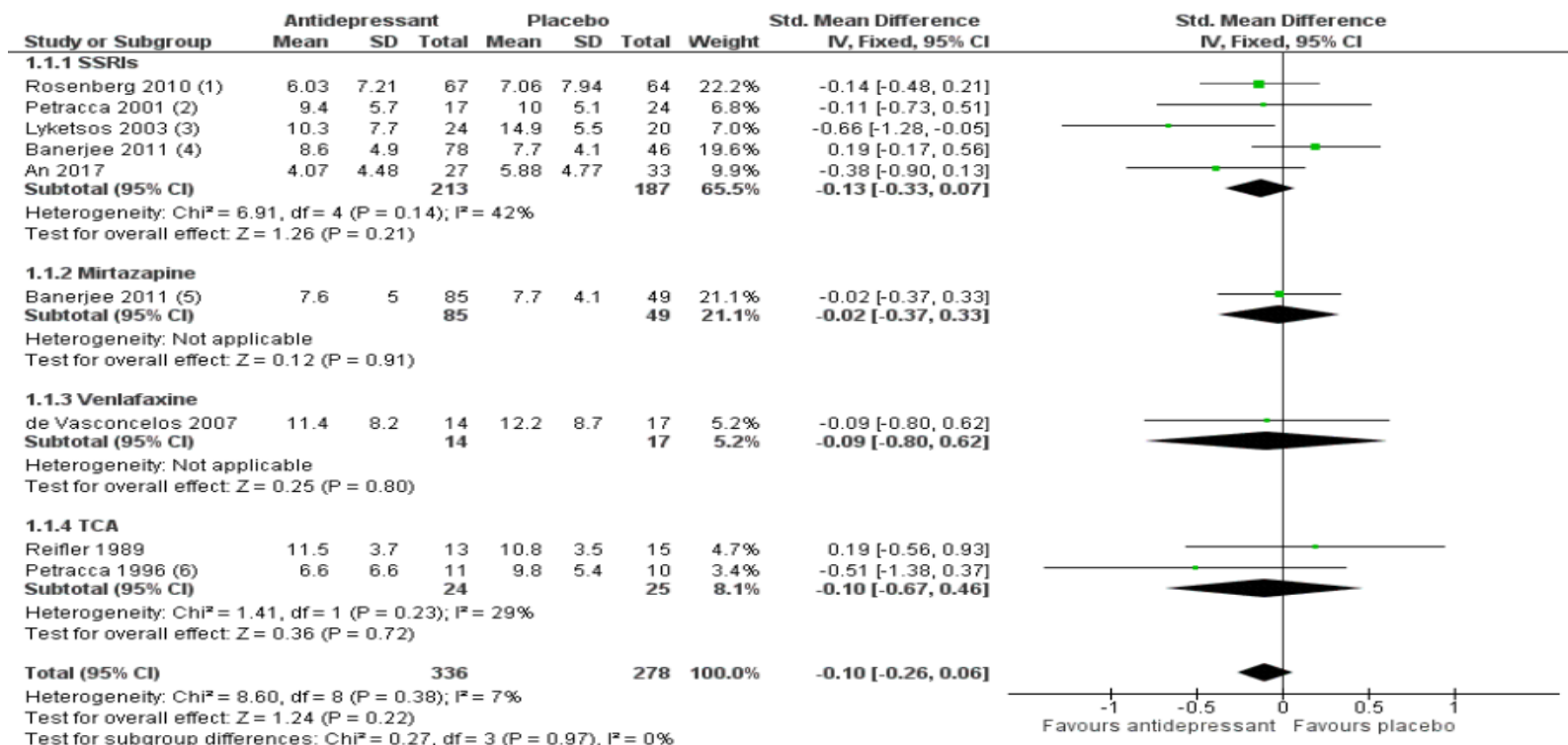

Fig. 4. Forest plot of comparison of antidepressants versus placebo: Cognition MMSE scores (6–13 weeks).

2018

Antidepressants for treating depression in dementia (Review)

Dudas R, Malouf R, McCleery J, Dening T

Study or Subgroup	Antidepressant Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
1.1.1 SSRIs									
Rosenberg 2010 (1)	6.03	7.21	67	7.06	7.94	64	22.2%	-0.14 [-0.48, 0.21]	
Petracca 2001 (2)	9.4	5.7	17	10	5.1	24	6.8%	-0.11 [-0.73, 0.51]	
Lyketsos 2003 (3)	10.3	7.7	24	14.9	5.5	20	7.0%	-0.66 [-1.28, -0.05]	
Banerjee 2011 (4)	8.6	4.9	78	7.7	4.1	46	19.6%	0.19 [-0.17, 0.56]	
An 2017	4.07	4.48	27	5.88	4.77	33	9.9%	-0.38 [-0.90, 0.13]	
Subtotal (95% CI)			**213**			**187**	**65.5%**	**-0.13 [-0.33, 0.07]**	
Heterogeneity: Chi² = 6.91, df = 4 (P = 0.14); I² = 42%									
Test for overall effect: Z = 1.26 (P = 0.21)									
1.1.2 Mirtazapine									
Banerjee 2011 (5)	7.6	5	85	7.7	4.1	49	21.1%	-0.02 [-0.37, 0.33]	
Subtotal (95% CI)			**85**			**49**	**21.1%**	**-0.02 [-0.37, 0.33]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.12 (P = 0.91)									
1.1.3 Venlafaxine									
de Vasconcelos 2007	11.4	8.2	14	12.2	8.7	17	5.2%	-0.09 [-0.80, 0.62]	
Subtotal (95% CI)			**14**			**17**	**5.2%**	**-0.09 [-0.80, 0.62]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.25 (P = 0.80)									
1.1.4 TCA									
Reifler 1989	11.5	3.7	13	10.8	3.5	15	4.7%	0.19 [-0.56, 0.93]	
Petracca 1996 (6)	6.6	6.6	11	9.8	5.4	10	3.4%	-0.51 [-1.38, 0.37]	
Subtotal (95% CI)			**24**			**25**	**8.1%**	**-0.10 [-0.67, 0.46]**	
Heterogeneity: Chi² = 1.41, df = 1 (P = 0.23); I² = 29%									
Test for overall effect: Z = 0.36 (P = 0.72)									
Total (95% CI)			**336**			**278**	**100.0%**	**-0.10 [-0.26, 0.06]**	
Heterogeneity: Chi² = 8.60, df = 8 (P = 0.38); I² = 7%									
Test for overall effect: Z = 1.24 (P = 0.22)									
Test for subgroup differences: Chi² = 0.27, df = 3 (P = 0.97), I² = 0%									

-1   -0.5   0   0.5   1
Favours antidepressant   Favours placebo

Footnotes

(1) Endpoint median values and interquartile ranges were calculated from Figure 2 of the original publication.
(2) ITT-LOCF data
(3) CSDD endpoint mean scores
(4) sertraline group
(5) mirtazapine group
(6) Endpoint mean values from Figure 1 of the original publication, assuming that the SDs remained the same.

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

2017-12

Dementia prevention, intervention, and care

Livingston, G

Revista de Psiquiatría y Salud Mental

ELSEVIER

Revista de Psiquiatría y Salud Mental

REVIEW ARTICLE

Tianeptine, an atypical pharmacological approach to depression☆

Cecilio Alamo[a,*], Pilar García-Garcia[a], Francisco Lopez-Muñoz[b,c], Cristina Zaragozá[a]

Journal of Affective Disorders

ELSEVIER

Research paper

The effects of vortioxetine on cognitive dysfunction in patients with inadequate response to current antidepressants in major depressive disorder: A short-term, randomized, double-blind, exploratory study versus escitalopram

Eduard Vieta[a,*], Lasse B. Sluth[b], Christina K. Olsen[b]

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[b] H. Lundbeck A/S, Valby, Denmark

ARTICLE INFO

ABSTRACT

Background: Major Depressive Disorder (MDD) is a heterogeneous disease characterized by emotional, physical and cognitive symptoms. This study explored the effects of vortioxetine versus escitalopram on outcomes of cognition, functioning and mood symptoms in depressed patients with inadequate response to current antidepressant treatment.

Methods: In this parallel-group, active-comparator study, adult patients (18–65 years, N = 101) with MDD, with inadequate response to current antidepressant monotherapy, were randomized 1:1 to 8 weeks' double-blind treatment with flexible doses (10–20 mg/day) of either vortioxetine or escitalopram. Primary and key secondary efficacy measures were the Digit Symbol Substitution Test (DSST), analyzed using a mixed model for repeated measurements, and the University of San Diego Performance-based Skills Assessment – Brief (UPSA-B), analyzed using analysis of covariance (last observation carried forward method).

CrossMark

REVIEW ARTICLE

Vortioxetine: Clinical Pharmacokinetics and Drug Interactions

Grace Chen[1] · Astrid-Maria Højer[2] · Johan Areberg[2] · George Nomikos[3]
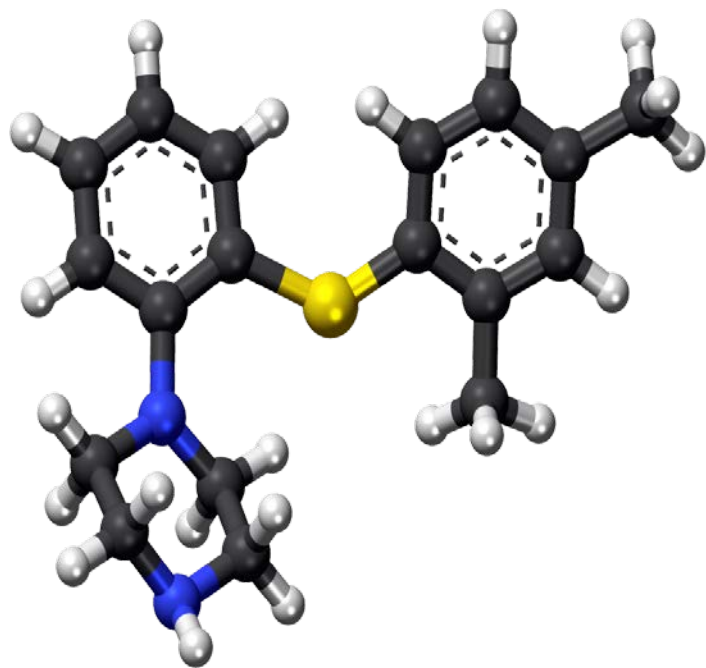
Key Points

Vortioxetine is an antidepressant with multimodal activity currently approved for the treatment of major depressive disorder at a dosage of 5–20 mg/day.

Vortioxetine has a favorable pharmacokinetic profile with dose-proportional and linear exposure, moderate oral bioavailability (75%; independent of food), extensive tissue distribution (steady-state volume of distribution of approximately 2600 L), and a long elimination half-life (66 h).

Concomitant therapy is generally well tolerated and dosage adjustments may be required when vortioxetine is co-administered with bupropion or rifampin.

REVIEW ARTICLE

Tianeptine, an atypical pharmacological approach to depression ☆

Cecilio Alamo [a,*], Pilar García-García [a], Francisco Lopez-Muñoz [b,c], Cristina Zaragozá [a]
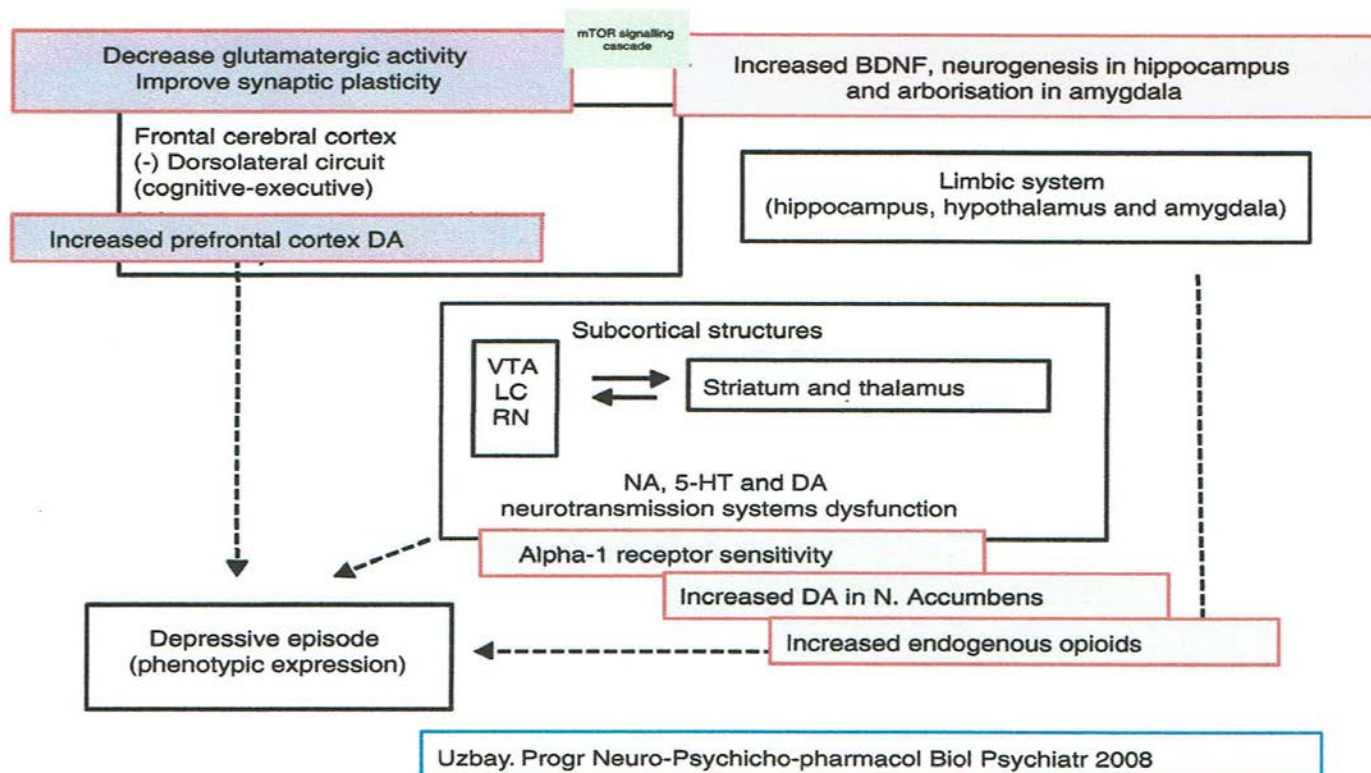
Figure 2 Mechanisms involved in the antidepressant effects of tianeptine.

Treatment Effects of Vortioxetine on Cognitive Functions in Mild Alzheimer's Disease Patients with Depressive Symptoms: A 12 Month, Open-Label, Observational Study

E. Cumbo, S. Cumbo, S. Torregrossa, D. Migliore

Table 1. Demographic and clinical characteristics of patients at baseline

Variable	Vortioxetine group (n= 36)	Control group (n=72)	Overall (n=108)
Females, n (%)	22 (61.1)	49 (68.1)	71 (65.7)
Males, n (%)	14 (38.9)	23 (31.9)	37 (34.2)
Race, Caucasian, n (%)	36 (100)	72 (100)	108 (100)
Age, yrs (mean ± SD)	76.5 ± 4.4	76.9 ± 4.1	76.7 ± 4.3
Length of education, yrs (mean ± SD)	5.9 ± 3.1	5.8 ± 3.2	5.8 ± 3.2
APOEε4 carrier, n (%)			
No	19 (54.28)	39 (55.71)	58 (55.2)
Yes	16 (47.71)	31 (44.28)	47 (44.8)
IADL score, (mean ± SD / total)	5.3 /8 ± 2.3	5.2 /8 ± 2.4	5.2 /8 ± 2.5
ADL score, (mean ± SD / total)	5.6 /6 ± 1.3	5.3 /6 ± 1.5	5.4 /6 ± 1.4
HIS score, (mean ± SD / total)	3.4 /18 ± 1.4	3.7 /18 ± 1.1	3.6 /18 ± 1.2
MMSE score, (mean ± SD / total)	20.87 /30 ± 3.2	20.79 /30 ± 3.3	20.83 /30 ± 3.4
GDS (short form) score, (mean ± SD / total)	8.82 /15 ± 2.4	8.61 /15 ± 2.6	8.71 /15 ± 2.5

Table 2. Rating scale score changes in vortioxetine and control groups

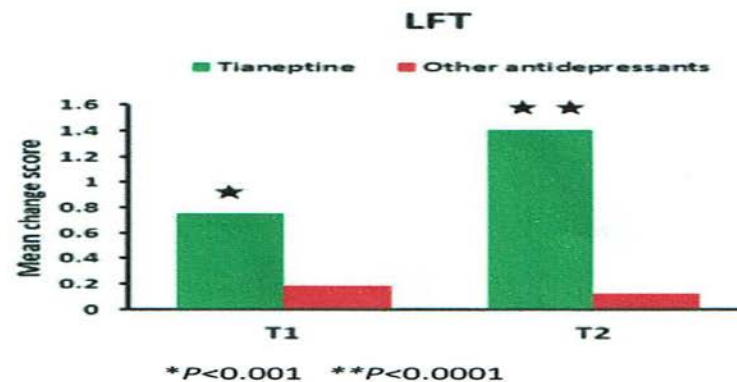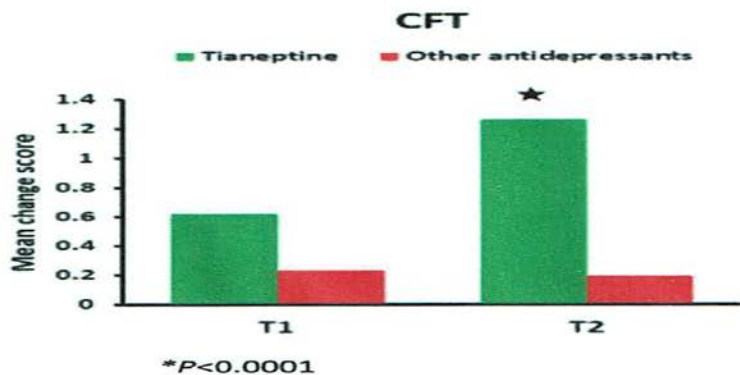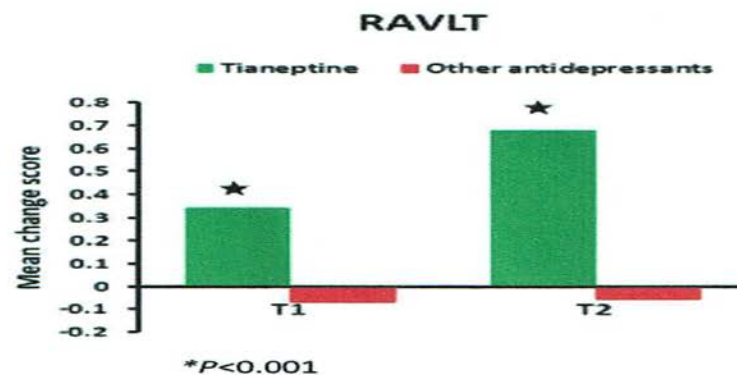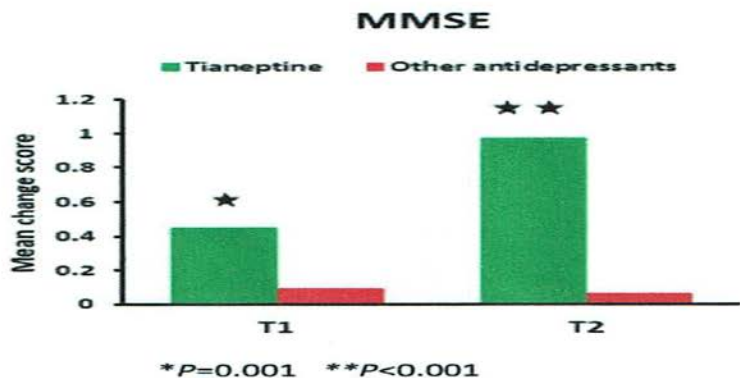| Variable	T0	T1	T2	Difference (T0-T2)	P value ANCOVA	P value Wilkoxson rank test
RCPM						
Vortioxetine group	11.65 ± 9.6	15.32 ± 10.4	15.36 ± 10.5	3.71	<0.001	<0.001
Control group	11.32 ± 9.4	12.87 ± 9.6	12.89 ± 9.7	1.56	0.925	0.879
ATTENTIVE MATRICES						
Vortioxetine group	25.74 ± 8.9	29.32 ± 10.2	29.36 ± 10.4	3.62	<0.001	<0.001
Control group	25.94 ± 8.9	26.61 ± 9.8	26.6 2 ± 9.9	0.68	0.879	0.694
DIGIT SPAN						
Vortioxetine group	3.4 ± 1.4	3.8 ± 1.6	3.9 ± 1.6	0.5	0.898	0.818
Control group	3.4 ± 1.3	3.6 ± 1.5	3.7 ± 1.6	0.3	0.949	0.922
MMSE						
Vortioxetine group	20.87 ± 3.2	23.98 ± 3.9	23.78 ± 3.8	2.91	<0.001	<0.001
Control group	20.79 ± 3.3	22.10 ± 3.7	21.20 ± 3.6	0.41	0.793	0.648
HAM-D						
Vortioxetine group	13.94 ± 4.5	6.53 ± 4.2	6.54 ± 4.1	- 7.40	<0.001	<0.001
Control group	13.51 ± 4.8	9.69 ± 4.6	9.70 ± 4.5	- 2.81	<0.001	<0.001
CSDD						
Vortioxetine group	13.82 ± 4.2	6.12 ± 3.2	6.14 ± 3.6	- 7.68	<0.001	<0.001
Control group	13.97 ± 4.2	9.30 ± 3.8	9.34 ± 3.7	- 4.63	<0.001	<0.001

Effects of Tianeptine Treatment on Depression and Cognitive Function in Patients with Alzheimer's Disease: A 12-Month Retrospective Observational Study

José María García-Alberca*, Esther Gris, Paz de la Guía and Silvia Mendoza
Alzheimer Research Center and Memory Clinic, Instituto Andaluz de Neurociencia (IANEC), Málaga, Spain

Table 2
Neuropsychological, neuropsychiatric, and functional performance of patients at baseline

Variable	Overall (n = 126)	Tianeptine group (n = 38)	Other antidepressants group (n = 88)	p
MMSE	20.88 ± 2.00	21.11 ± 1.79	20.78 ± 2.09	0.384
RAVLT	18.34 ± 2.88	18.84 ± 2.64	18.13 ± 2.97	0.181
CFT	8.83 ± 1.09	8.87 ± 0.70	8.81 ± 1.22	0.723
LFT	8.67 ± 1.06	8.89 ± 0.95	8.57 ± 1.09	0.095
TMTA	162.44 ± 22.14	160.82 ± 21.42	163.15 ± 22.52	0.583
TMTB	245.94 ± 31.24	251.32 ± 28.52	243.61 ± 32.21	0.185
SDMT	24.17 ± 8.20	24.26 ± 4.38	24.14 ± 9.40	0.918
BNT	10.13 ± 1.58	9.84 ± 0.89	10.25 ± 1.79	0.090
NPI	22.44 ± 3.53	21.95 ± 3.04	22.66 ± 3.72	0.264
NPI-D	4.02 ± 1.30	4.13 ± 1.21	3.97 ± 1.34	0.498
HDRS	14.87 ± 4.12	14.00 ± 4.60	15.24 ± 3.86	0.152
CSDD	15.69 ± 4.27	15.34 ± 4.95	15.84 ± 3.97	0.585
IDDD	52.13 ± 13.17	51.71 ± 13.61	52.31 ± 13.04	0.820

Results from the linear mixed model

MMSE
*P=0.001   **P<0.001

RAVLT
*P<0.001

CFT
*P<0.0001

LFT
*P<0.001   **P<0.0001

BNT
*P<0.001

NPI-D
*P<0.0001
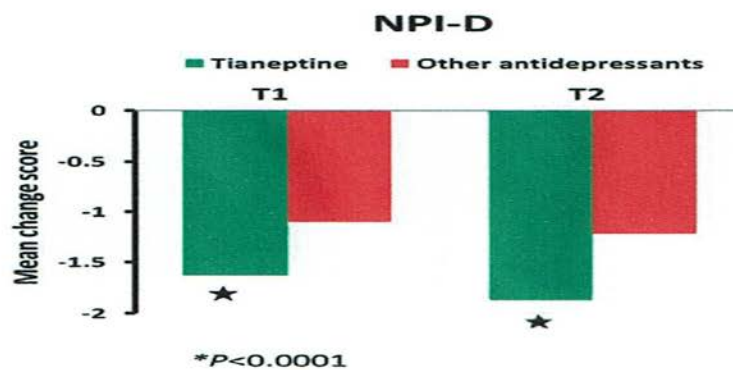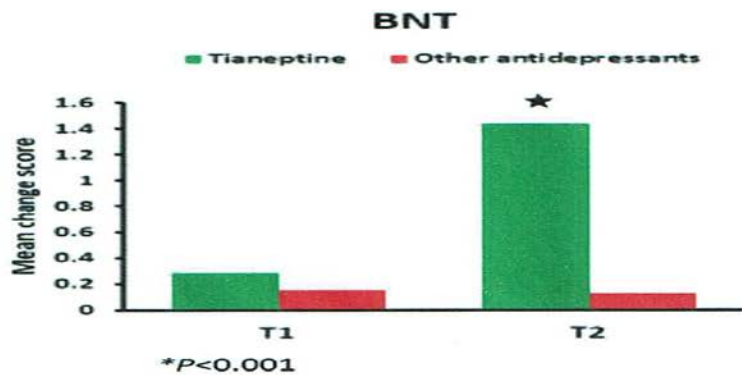
PRIMERA

La depresión es frecuente en la EA y se asocia con una mayor discapacidad, peor calidad y menor esperanza de vida.

Los antidepresivos se prescriben con frecuencia para su tratamiento.

SEGUNDA

Las pruebas sobre las tasas de remisión favorecen a los antidepresivos, pero la evidencia es de calidad moderada y no proporciona un fuerte apoyo a la eficacia de los antidepresivos para el tratamiento de la depresión en la EA, especialmente después de 12 semanas.

TERCERA

Nuevos antidepresivos atípicos o de acción multimodal, como tianeptina y vortioxetina, pueden contribuir a reducir la sintomatología depresiva y mejorar la función cognitiva en pacientes con EA.

Estos efectos positivos probablemente proporcionan beneficios adicionales al dirigirse a mecanismos fisiopatológicos diferentes en comparación con otros antidepresivos.

CUARTA

Estos resultados deberían inspirar el diseño de futuros ensayos controlados a largo plazo que contribuyan a respaldar el uso de estos nuevos antidepresivos para mejorar la función cognitiva en pacientes con EA. Además, este estudio podría ayudar a los clínicos en el tratamiento de la EA y beneficiar a los pacientes afectados.